Saidha, Tekchand

To: STIC-ILL
Subject: art request - 09/837235

A copy of the following refrence(s) is requested :

1. ANSWER 6 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1982:300038 BIOSIS
DOCUMENT NUMBER: BA74:72518
TITLE: OZONE INDUCED FORMATION OF O O' **DI TYROSINE** CROSS LINKS IN PROTEINS.
AUTHOR(S): VERWEIJ H; CHRISTIANSE K; VAN STEVENINCK J
CORPORATE SOURCE: SYLVIUS LAB., DEP. MED. BIOCHEMISTRY, WASSENAARSEWEG 72, 2333 AL LEIDEN.
SOURCE: **BIOCHIM BIOPHYS ACTA, (1982) 701 (2), 180-184.**

2. TITLE: CHEMICAL NATURE OF MONOGENEAN SCLERITES PART 1 STABILIZATION OF CLAMP **PROTEIN** BY FORMATION OF **DI TYROSINE**.
AUTHOR(S): RAMALINGAM K
SOURCE: PARASITOLOGY, (1973) 66 (1), 1-7.
CODEN: PARAAE. ISSN: 0031-1820.

TITLE: CD and proton NMR studies on the side-chain conformation of tyrosine derivatives and tyrosine residues in di- and tripeptides
AUTHOR(S): Juy, Michel; Lam Thanh Hung; Fermandjian, Serge
CORPORATE SOURCE: Dep. Biol., Cent. Nucl. Stud., Gif-sur-Yvette, 91191, Fr.
SOURCE: **International Journal of Peptide & Protein Research (1982), 20(4), 298-307**

3. Journal of the American Chemical Society (1985), 107(3), 659-66

4. **BIOCHEMICAL JOURNAL**, (2003 Mar 1) 370 (Pt 2) 729-35.

5. Salt-**stabilized protein** formulation

SOURCE: **Research Disclosure (1995), 370, 56-7**

Thank you !

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Brief Summary Text (9):
The cDNA-derived amino acid sequence, reported by Johnston, et al., in Cell 56, 1033-1044 (Mar. 24, 1989), and in U.S. Ser. No. 07/320,408 filed Mar. 8, 1989, indicates that it contains a number of modular domains that are likely to fold independently. Beginning at the N-terminus, these include a "lectin" domain, an "EGF" domain, nine tandem consensus repeats similar to those in complement binding proteins, a transmembrane domain (except in a soluble form that appears to result from differential splicing), and a cytoplasmic tail.

Brief Summary Text (12):
Peptides derived from P-selectin are described in U.S. Ser. No. 07/554,199 entitled "Functionally Active Selectin-Derived Peptides" filed Jul. 17, 1990 by Rodger P. McEver that are useful in diagnostics and in modulating the hemostatic and inflammatory responses in a patient wherein a therapeutically effective amount of a peptide capable of blocking leukocyte recognition of P-selectin is administered to the patient. U.S. Ser. No. 07/554,199 filed Jul. 17, 1990 also discloses that peptide sequences within the lectin domain of P-selectin, having homology with the lectin domains of other proteins, especially E-selectin and the L-selectin, selectively inhibit neutrophil adhesion to purified P-selectin, and can therefore be used in diagnostic assays of patients and diseases characterized by altered binding by these molecules, in screening assays for compounds altering this binding, and in clinical applications to inhibit or modulate interactions of leukocytes with platelets or endothelial cells involving coagulation and/or inflammatory processes.

Brief Summary Text (13):
E-selectin, L-selectin, and P-selectin have been termed "selecting", based on their related structure and function. E-selectin is not present in unstimulated endothelium. However, when endothelium is exposed to cytokines such as tumor necrosis factor of interleukin-1, the gene for E-selectin is transcribed, producing RNA which in turn is translated into protein. The result is that E-selectin is expressed on the surface of endothelial cells one to four hours after exposure to cytokines, as reported by Bevilacqua et al., Proc.Natl.Acad.Sci.USA 84: 9238-9242 (1987) (in contrast to P-selectin, which is stored in granules and presented on the cell surface within seconds after activation). E-selectin has been shown to mediate the adherence of neutrophils to cytokine-treated endothelium and thus appears to be important in allowing leukocytes to migrate across cytokine-stimulated endothelium into tissues. The cDNA-derived primary structure of E-selectin indicates that it contains a "lectin" domain, an EGF domain, and six (instead of the nine in P-selectin) repeats similar to those of complement-regulatory proteins, a transmembrane domain, and a short cytoplasmic tail. There is extensive sequence homology between P-selectin and E-selectin throughout both proteins, but the similarity is particularly striking in the lectin and EGF domains.

Brief Summary Text (18):
Proteins involved in the hemostatic and inflammatory pathways are of interest for diagnostic purposes and treatment of human disorders. However, there are many problems using proteins therapeutically. Proteins are usually expensive to produce in quantities sufficient for administration to a patient. Moreover, there can be a reaction against the protein after it has been administered more than once to the patient. It is therefore desirable to develop peptides having the same, or better, activity as the protein, which are inexpensive to synthesize, reproducible and relatively innocuous.

Brief Summary Text (19):
It is preferable to develop peptides which can be prepared synthetically, having activity at least equal to, or greater than, the peptides derived from the protein itself.

Brief Summary Text (46):
Peptides of the invention have as their core region portions of the 42-48 amino acid sequences of the selectins, with residue 1 defined as the N-terminus of the mature proteins after the cleavage of the signal peptides.

Detailed Description Text (23):

Still additional preferred peptides are those of Formula III where Y.sup.3 is selected from the group consisting of Tyr-Tyr-Val, Tyr-Tyr, Tyr, and null (signifying no amino acid), wherein each of the amino acids may be a D- or L-amino acid.

Detailed Description Text (46):
The peptides can also be prepared using standard genetic engineering techniques known to those skilled in the art. For example, the peptide can be produced enzymatically by inserting nucleic acid encoding the peptide into an expression vector, expressing the DNA, and translating the DNA into the peptide in the presence of the required amino acids. The peptide is then purified using chromatographic or electrophoretic techniques, or by means of a carrier protein which can be fused to, and subsequently cleaved from, the peptide by inserting into the expression vector in phase with the peptide encoding sequence a nucleic acid sequence encoding the carrier protein. The fusion protein-peptide may be isolated using chromatographic, electrophoretic or immunological techniques (such as binding to a resin via an antibody to the carrier protein). The peptide can be cleaved using chemical methodology or enzymatically, as by, for example, hydrolases.

Detailed Description Text (54):
Alternatively, the peptide may be administered in liposomes or microspheres (or microparticles). Methods for preparing liposomes and microspheres for administration to a patient are known to those skilled in the art. U.S. Pat. No. 4,789,734 describes methods for encapsulating biological materials in liposomes. Essentially, the material is dissolved in an aqueous solution, the appropriate phospholipids and lipids added, along with surfactants if required, and the material dialyzed or sonicated, as necessary. A review of known methods is by G. Gregoriadis, Chapter 14, "Liposomes", Drug Carriers in Biology and Medicine, pp. 287-341 (Academic Press, 1979). Microspheres formed of polymers or proteins are well known to those skilled in the art, and can be tailored for passage through the gastrointestinal tract directly into the bloodstream. Alternatively, the peptide can be incorporated and the microspheres, or composite of microspheres, implanted for slow release over a period of time, ranging from days to months. See, for example, U.S. Pat. Nos. 4,906,474, 4,925,673 and 3,625,214.

Detailed Description Text (59):
Human neutrophils are isolated from heparinized whole blood by density gradient centrifugation on Mono-Poly resolving media, Flow Laboratories. Neutrophil suspensions are greater than 98% pure and greater than 95% viable by trypan blue exclusion. For adhesion assays, neutrophils are suspended at a concentration of 2.times.10.sup.6 cells/mL in Hanks' balanced salt solution containing 1.26 mM Ca.sup.2+ and 0.81 mM Mg.sup.2+ (HBSS, Gibco) with g mg/mL human serum albumin (HBSS/HSA). Adhesion assays are conducted in triplicate in 96-well microtiter plates, Corning, incubated at 4.degree. C. overnight with 50 microliters of various protein solutions.

Detailed Description Text (60):
P-selectin is isolated from human platelet lysates by immunoaffinity chromatography on antibody S12-Sepharose.TM. and ion-exchange chromatography on a Mono-Q.TM. column (FLPC, Pharmacia Fine Chemicals), as follows.

Detailed Description Text (63):
The soluble fraction (0.5 M NaCl wash) and the membrane extract (also adjusted to 0.5 M NaCl) are absorbed with separate pools of the monoclonal antibody S12 (directed to P-selectin) previously coupled to Affigel (Biorad) at 5 mg/mL for 2 hours at 4.degree. C. After letting the resins settle, the supernatants are removed. The S12 Affigel containing bound GMP-140 is then loaded into a column and washed overnight at 4.degree. C. with 400 mL of 0.5 M NaCl, 20 mM Tris pH 7.5, 0.01% Lubrol PX.

Detailed Description Text (64):
Bound P-selectin is eluted from the S12 Affigel with 100 mL of 80% ethylene glycol, 1 mM MES pH 6.0, 0.01% Lubrol PX. Peak fractions with absorbance at 280 nm are pooled. Eluates are dialyzed against TBS with 0.05% Lubrol, then applied to a Mono Q column (FPLC from Pharmacia). The concentrated protein is step eluted with 2 M NaCl, 20 mM Tris pH 7.5 (plus 0.05% Lubrol PX for the membrane fraction). Peak fractions are dialyzed into TBS pH 7.5 (plus 0.05% Lubrol PX for the membrane fraction).

Detailed Description Text (65):
P-selectin is plated at 5 micrograms/mL and the control proteins: human serum albumin (Alb), platelet glycoprotein IIb/IIIa (IIb), von Willebrand factor (vWF), fibrinogen (FIB), thrombomodulin (TM), gelatin (GEL) or human serum (HS), are added at 50 micrograms/mL. All wells are blocked for 2 hours at 22.degree. C. with 300 microliters HBSS containing 10 mg/mL HSA, then washed three times with HBSS containing 0.1% Tween-20 and once with HBSS. Cells (2.times.10.sup.5 per well) are added to the wells and incubated at 22.degree. C. for 20 minutes. The wells are then filled with HBSS/HSA, sealed with acetate tape (Dynatech), and centrifuged inverted at 150 g for 5 minutes. After discarding nonadherent cells and supernates, the contents of each well are solubilized with 200 microliters 0.5% hexadecyltrimethylammonium bromide, Sigma, in 50 mM potassium phosphate, pH. 6.0, and assayed for myeloperoxidase activity, Ley, et al., Blood 73, 1324-1330 (1989). The number of cells bound is derived from a standard curve of myeloperoxidase activity versus numbers of cells. Under all assay conditions, the cells release less than 5% of total myeloperoxidase and lactate dehydrogenase. Inhibition is read as a lower percent adhesion, so that a value of 5% means that 95% of the specific adhesion was inhibited.

Detailed Description Text (79):
The peptides can also be used for the detection of human disorders in which the ligands for the selectins might be defective. Such disorders would most likely be seen in patients with increased susceptibility to infections in which leukocytes might not be able to bind to activated platelets or endothelium. Cells to be tested, usually leukocytes, are collected by standard medically approved techniques and screened. Detection systems include ELISA procedures, binding of radiolabeled antibody to immobilized activated cells, flow cytometry, or other methods known to those skilled in the art. Inhibition of binding in the presence and absence of the lectin domain peptides can be used to detect defects or alterations in selectin binding. For selectins, such disorders would most likely be seen in patients with increased susceptibility to infections in which leukocytes would have defective binding to platelets and endothelium because of deficient leukocyte ligands for P-selectin.

Detailed Description Text (80):
The peptide is labeled radioactively, with a fluorescent tag, enzymatically, or with electron dense material such as gold for electron microscopy. The cells to be examined, usually leukocytes, are incubated with the labeled peptides and binding assessed by methods described above with antibodies to P-selectin, or by other methods known to those skilled in the art. If ligands for P-selectin are also found in the plasma, they can also be measured with standard ELISA or radioimmunoassay procedures, using labeled P-selectin-derived peptide instead of antibody as the detecting reagent.

Detailed Description Paragraph Table (1):

(SEQ ID NO: 1) Asp--Tyr--Leu--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr--Val-NH.sub.2 ; (SEQ ID NO: 2)
Tyr--Leu--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr--Val-NH.sub.2 ; (SEQ ID NO: 3) Leu--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr--Val-NH.sub.2 ; (SEQ ID NO: 4) Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr--Val-NH.sub.2 ; (SEQ ID NO: 5) Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr--Val-NH.sub.2 ; (SEQ ID NO: 6) Asp--Tyr--Leu--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 7) Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 8) Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 9)
Lys--Thr--Leu--Pro--Phe--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 10)
Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr--Val-NH.sub.2 ; (SEQ ID NO: 11)
Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr-NH.sub.2 ; (SEQ ID NO: 12)
Lys--Val--Leu--Ala--Tyr--Tyr--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 13)
Lys--Val--Leu--Pro--Ala--Tyr--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 14)
Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ala--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 15)
Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Ala--Tyr-NH.sub.2 ; (SEQ ID NO: 16)
Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Thr--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 17)
Lys--Val--Leu--Pro--Tyr--Tyr--Thr--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 18)
Asp--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 19)
Lys--Val--Leu--Pro--Tyr--Gly--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 20)
Lys--Val--Leu--Pro--Arg--Tyr--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 21)

Asn--Thr--Leu--Pro--Tyr--Ser--Pro--Tyr--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 22)
Lys--Val--Gln--Pro--Tyr--Tyr--Ser--Ser--Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 23)
Glu--Tyr--Leu--Asn--Ser--Ile--Leu--Ser--Tyr--Ser--Pro--Ser--Tyr--T yr--Trp-NH.sub.2 ;
(SEQ ID NO: 24) Asp--Tyr-cyclo(Cys--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--C
ys)--Tyr--Val-NH.sub.2 ; (SEQ ID NO: 25)
Tyr-cyclo(Cys--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Cys)-- Tyr--Val-NH.sub.2 ;
(SEQ ID NO: 26) Asp--Tyr-cyclo(Cys--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--C
ys)--Tyr-NH.sub.2 ; (SEQ ID NO: 27)
Asp--Tyr-cyclo(Cys--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--C ys)-NH.sub.2 ; (SEQ
ID NO: 28) Tyr-cyclo(Cys--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Cys)--
Tyr-NH.sub.2 ; (SEQ ID NO: 29)
cyclo(Cys--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Cys)--Tyr- -Val-NH.sub.2 ;
(SEQ ID NO: 30) cyclo(Cys--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Cys)--Tyr-
NH.sub.2 ; (SEQ ID NO: 31)
cyclo(Cys--Asn--Lys--Val--Leu--Pro--Tyr--Tyr--Ser--Ser--Cys)-NH.su b.2 ; (SEQ ID NO:
32) Asp--Tyr--Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--
Tyr--Tyr--Val-NH.sub.2 ; (SEQ ID NO: 33)
Tyr--Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--Tyr-- Tyr--Val-NH.sub.2 ;
(SEQ ID NO: 34) Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--Tyr--Tyr--
Val-NH.sub.2 ; (SEQ ID NO: 35)
Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--Tyr--Tyr--Val-N H.sub.2 ; (SEQ ID
NO: 36) Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--Tyr--Tyr--Val-NH.sub .2 ; (SEQ
ID NO: 37) Asp--Tyr--Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--
Tyr--Tyr-NH.sub.2 ; (SEQ ID NO: 38)
Asp--Tyr--Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)-- Tyr-NH.sub.2 ; (SEQ
ID NO: 39) Asp--Tyr--Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)-N H.sub.2
; (SEQ ID NO: 40) Tyr--Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--Tyr--
Tyr-NH.sub.2 ; (SEQ ID NO: 41)
Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--Tyr--Tyr-N H.sub.2 ; (SEQ ID
NO: 42) Leu--Asn--Lys--Val-cyclo(Cys--Pro--Tyr--Tyr--Ser--Cys)--Tyr-NH.sub .2.

Other Reference Publication (140):
Aruffo, A. et al., "Granule Membrane Protein 140 (GMP140) Binds to Carcinomas and Carcinoma-Derived Cell Lines", PNAS USA 1992, 89, 2292-2296.

Other Reference Publication (141):
Heavner, G. et al., "Peptides from Multiple Regions of the Lectin Domain of P-Selectin Inhibiting Neutrophil Adhesion", Int. J. Peptide Protein Res. 1993, 42, 484-489.